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Reversal of direct oral anticoagulants: Highlights from the Anticoagulation Forum guideline

ABSTRACT

The 2019 guideline from the Anticoagulation Forum provides clear instructions on how to use 2 agents for reversing the effects of direct oral anticoagulants (DOACs): idarucizumab for dabigatran-associated bleeding and andexanet alfa for bleeding associated with rivaroxaban and apixaban. The guideline also discusses off-label use of andexanet alfa for bleeding associated with edoxaban and betrixaban and the use of hemostatic agents such as activated prothrombin complex concentrate and 4-factor prothrombin complex concentrate. Lastly, it offers approaches for building and managing stewardship programs at the health system level.

KEY POINTS

- DOACs offer many advantages over warfarin.
- The number of patients treated with DOACs is increasing, as are rates of major and life-threatening DOAC-associated bleeding.
- Clear guidelines for the reversal of DOAC-associated bleeding are needed.
- Reversal agents are now commercially available and have demonstrated their ability to reverse the effects of DOACs.
- These agents are expensive and pose some thrombotic risk—thus the need for comprehensive reversal guidelines.

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Direct oral anticoagulants (DOACs) include dabigatran, which is a direct thrombin (factor IIa) inhibitor, and 4 direct factor Xa inhibitors: rivaroxaban, apixaban, edoxaban, and betrixaban. These agents have a number of approved indications, including prevention of systemic embolization and stroke in patients with nonvalvular atrial fibrillation, preventing and treating venous thromboembolism, and secondary prevention of arterial ischemic conditions in chronic coronary arterial disease and peripheral artery disease (**Table 1**).

Many clinical trials have shown DOACs to be noninferior to warfarin, and they offer many advantages over warfarin. They are associated with less intracranial bleeding, do not require routine blood monitoring, have fewer dietary and drug interactions, and have predictable pharmacokinetics with rapid onset of action.[1–3] Because they have short half-lives, they do not need bridging (ie, substitution of a shorter-acting agent) before surgical procedures for which anticoagulation must be interrupted, thereby significantly simplifying periprocedural planning.[4,5]

Since the number of patients treated with DOACs is increasing, major and life-threatening DOAC-associated bleeding has also been on the rise.

ANTICOAGULATION FORUM GUIDELINE

A 2019 guideline from the Anticoagulation Forum[6] provides clear instructions on how to manage DOAC-associated bleeding.

TABLE 1

Approved indications for direct oral anticoagulants

	Nonvalvular atrial fibrillation	Treatment of deep vein thrombosis or pulmonary embolism	Prevention of deep vein thrombosis in total knee replacement	Prevention of deep vein thrombosis in total hip replacement	Prevention of deep vein thrombosis in medically ill	Coronary artery disease or peripheral artery disease
Apixaban	Yes	Yes	Yes	Yes	No	No
Betrixaban	No	No	No	No	Yes	No
Dabigatran	Yes	Yes	No	Yes	No	No
Edoxaban	Yes	Yes	No	No	No	No
Rivaroxaban	Yes	Yes	Yes	Yes	No	Yes

Intended audience for the guideline

General practice, hematology, anticoagulation clinics, emergency, cardiovascular, surgical, and intensive care providers.

Authors of the guideline

The authors of the guideline are associated with the Anticoagulation Forum (acforum.org) and are recognized experts in the field. Conflicts of interest were disclosed when present.

Process used for writing the guideline

The unanimous consensus of all authors was determined for each question addressed. The authors conducted a PubMed search related to each key question by prioritizing studies involving patient-reported bleeding, thromboembolism, and mortality. In addition, they reviewed supplemental material of studies cited, US Food and Drug Administration (FDA) package inserts, and www.clinicaltrials.gov and also manually reviewed references.

MAIN RECOMMENDATIONS OF THE GUIDELINES

Available reversal agents

Two FDA-approved target-specific reversal agents are now commercially available.

Idarucizumab is a humanized monoclonal antidabigatran antibody fragment approved for reversing dabigatran-associated bleeding.[7]

Andexanet alfa is a modified recombinant inactive form of human factor Xa that binds to and blocks the effects of factor Xa inhibitors. It is approved for reversal of apixaban and rivaroxaban in cases of bleeding.[8] However, its use to reverse the effects of edoxaban and betrixaban is currently off-label, as larger studies are still needed to determine its efficacy and safety for this use.

Off-label use of hemostatic agents. The guideline also includes suggestions for off-label use of hemostatic agents such as activated prothrombin complex concentrate (APCC) for dabigatran-associated bleeding[8] and 4-factor prothrombin complex concentrate (4FPCC) for direct factor Xa inhibitor-associated bleeding.[9,10]

APCC contains a balanced ratio of the zymogen forms of factors II, VII, IX, and X (which are procoagulants); protein C (an anticoagulant); and tissue factor pathway inhibitor, cofactors V and VIII, and protein S.[9] In a prospective study,[10] it was associated with good hemostasis and no thromboembolic events.

4FPCC, which contains factors II, VII, IX, and X; proteins C and S; antithrombin III; and human albumin, can be considered for reversing direct factor Xa inhibitor-associated bleeding. However, in 2 studies,[11,12] 4FPCC

A 2019 guideline provides clear instructions on how to manage DOAC-associated bleeding

TABLE 2

When to give high vs low dose andexanet alfa infusion

Drug	Last dose	Time from last dose: < 8 hours or unknown	Time from last dose: ≥ 8 hours
Apixaban	≤ 5 mg	Low dose[a]	Low dose
	> 5 mg or unknown	High dose[b]	Low dose
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	Low dose

[a]Low dose: 400 mg intravenous bolus at a target rate of 30 mg/minute, followed by 4 mg/minute for up to 120 minutes.
[b]High dose: 800 mg intravenous bolus at a target rate of 30 mg/minute, followed by 8 mg/minute for up to 120 minutes.

The Joint Commission will require healthcare systems to have protocols for managing DOAC-related bleeding

was associated with ischemic stroke and thromboembolic events. Therefore, caution is needed when using this agent.

Supportive care should be considered in all cases of bleeding associated with DOACs. This includes stopping the DOAC, applying local hemostasis, transfusing red blood cells and platelets, and volume resuscitation.

Indications for reversal agents

The guideline does not recommend routinely using reversal agents for DOAC overdose, but strongly recommends using them only in cases of the following:

- Life-threatening bleeding
- Bleeding into critical organs
- Other major bleeding not controlled with maximal support measures (stopping the anticoagulant or other medications that prolong bleeding, compression or procedures to stop the bleeding at the bleeding site, volume resuscitation, or transfusion)
- Concerns or reasonable expectation that there is a clinically relevant plasma DOAC level
- Urgent invasive procedures in DOAC-treated patients, including cardiac, vascular, and neurosurgical emergency surgeries that need to be performed to save limbs, organs, or the life of the patient.[13]

Dosage

The guideline recommends the following in cases of major bleeding or to reverse anticoagulation for urgent procedures:

If the patient is taking dabigatran, give idarucizumab 5 g intravenously. If idarucizumab is not available, the alternative is APCC 50 units/kg intravenously (off-label use).

If taking rivaroxaban in doses of 10 mg or less or if the last dose of rivaroxaban was taken 8 or more hours ago, initiate andexanet alfa in a low dose, ie, 400 mg intravenous bolus at a target rate of 30 mg/minute followed by continuous infusion at 4 mg/minute for up to 120 minutes.

If the amount or time of the last dose is unknown or if it was more than 10 mg less than 8 hours ago, initiate high-dose andexanet alfa, ie, 800 mg intravenous bolus at a rate of 30 mg/minute followed by continuous infusion at 8 mg/minute for up to 120 minutes. If andexanet alfa is not available, the recommended alternative is 4FPCC 2,000 units intravenously (**Table 2**).

If taking apixaban in doses of 5 mg or less or if the last dose of apixaban was taken 8 or more hours ago, initiate low-dose andexanet alfa (400 mg intravenous bolus at a target rate of 30 mg/minute followed by continuous infusion at 4 mg/minute for up to 120 minutes). If the time or amount is unknown or the last dose was more than 5 mg and less than 8 hours ago, initiate high-dose andexanet alfa (800 mg intravenous bolus at a rate of 30 mg/minute followed by continuous infusion at 8 mg/minute for up to 120 minutes) (**Table 2**). If andexanet alfa is not available, the recommended alternative treatment is 4FPCC 2,000 units intravenously.

If taking edoxaban or bextrixaban, give andexanet alfa 800 mg intravenous bolus followed by continuous infusion of 8 mg/minute for up to 120 minute (off-label use) or 4FPCC 2,000 units intravenously (**Table 3**).

Concerns

The specific reversal agents that are available for dabigatran and anti-Xa inhibitors are of clear clinical benefit, as outlined above. However, the Anticoagulation Forum guideline expresses concern over the high cost of DOAC reversal agents, which may limit their availability. In addition, there is a risk of thrombosis associated with 4FPCC and andexanet alfa. Arterial and venous thrombosis, myocardial infarction,

TABLE 3

Reversal agents for dabigatran-, edoxaban- and betrixaban-related major bleeding or a required urgent procedure

DOAC	Reversal agent dosing
Dabigatran	Idarucizumab 5 g intravenously (IV) If idarucizumab is not available, the alternative treatment recommended is activated prothrombin complex concentrate 50 units/kg IV (off-label use)
Edoxaban, betrixaban	Andexanet alfa 800 mg IV bolus at 30 mg/minute followed by continuous infusion of 8 mg/minute for up to 120 minutes (off-label use) or 4-factor prothrombin complex concentrate 2,000 units IV

ischemic stroke, cardiac arrest or sudden death were observed within 3 to 30 days post administration of 4FCC[11] and andexanet alfa[8] (median time to the first event was 7 days).

With idarucizumab treatment, rates of thrombotic events (venous thromboembolism, ischemic stroke, myocardial infarction, and systemic embolism) were 4.8% at 30 days and 6.8% at 90 days. However, the study reported that events at 30 days may have been caused by the low level of restarting anticoagulation treatment. Thrombotic events at 90 days were likely associated with the underlying prothrombotic medical conditions rather than idarucizumab treatment.[7]

With APPC treatment, there were no thrombotic events reported.[10] However, postmarketing surveillance reported thromboembolic events especially after high doses and in patients with thromboembolic risk factors.[14]

Therefore, the benefit of reversing anticoagulation therapy must be carefully weighed against the risk of thromboembolic events. Proper anticoagulation should be resumed once the risk of thromboembolism outweighs the risk of bleeding. The patient should be monitored for possible thromboembolic events during and after the administration of a reversal agent.

Stewardship programs

Finally, the guideline authors recommend that health systems focus on building a stewardship program to address challenging DOAC reversal cases appropriately. Most of the potential challenges can be placed into the categories of acquisition and cost, operational logistics, and appropriate utilizations. A stewardship team dedicated to developing, implementing, and maintaining system-wide processes and protocols pertaining to optimal utilization of DOAC reversal agents has been shown to be effective in overcoming these challenges.

DIFFERENCES WITH EARLIER GUIDELINES, AND EXPECTED CLINICAL IMPACT

The Anticoagulation Forum guideline provides a rational, systematic, clinical approach for treating DOAC-associated bleeding with idarucizumab and andexanet alfa. Before it was published, 2 pivotal guidelines discussed anticoagulant reversal strategies, 1 from the American College of Cardiology in 2017[4] and the other from the European Heart Rhythm Association in 2018.[13]

In 2 studies, 4FPCC was associated with ischemic stroke and thromboembolic events

Newer agent. These two guidelines were published before the FDA approved andexanet alfa and therefore did not contain comprehensive dosing information and recommendations on using it in reversing the effects of DOACs. Despite this difference, they offer valuable clinical information that supplements the Anticoagulation Forum guideline.

Laboratory tests. The American College of Cardiology paper,[4] which covered all oral anticoagulants, including warfarin, discussed using various laboratory tests to determine the anticoagulant levels. These laboratory tests included:

- Dilute thrombin time, ecarin clotting time, or ecarin chromogenic assay. A prolonged time or elevated assay suggests possible dabigatran overdose.

TABLE 4

Dosing of antifibrinolytic agents

Tranexamic acid	1–1.5 g orally every 8–12 hours for duration of bleeding
	10-20 mg/kg intravenous (IV) bolus followed by 10 mg/kg IV every 6–8 hours for major bleeding, hemophilic bleeding, or after major trauma
	Longer intervals for renal insufficiency
Epsilon-aminocaproic acid	3 g orally 3–4 times per day
	2 g IV every 6 hours or 1 g IV every hour, depending on the urgency
Desmopressin	0.3 µg/kg subcutaneously
	0.3 µg/kg IV in 50 mL of normal saline over 15–30 minutes

Information from reference 17.

- Chromogenic anti-Xa assay. Absence of chromogenic anti-Xa activity indicates a possible absence of clinically relevant apixaban, rivaroxaban, or edoxaban levels.
- Activated partial thromboplastin time. Prolonged time suggests a possible overdose.
- Prothrombin time. Prolonged prothrombin time suggests a possible overdose of apixaban, rivaroxaban, or edoxaban.

Special populations. The European Heart Rhythm Association's guideline[13] contained important clinical information on the use of DOACs in special patient populations such as fragile and older patients, patients with extreme body weights, and patients with epilepsy and malignancy.

Other agents. Additionally, unlike the US guidelines, the European guideline[13] supports diuresis with intravenous fluids for dabigatran overdose and antifibrinolytic agents in the setting of non–life-threatening major bleeding.

Hospital protocols. As DOACs become more widely prescribed, health systems will need to establish comprehensive evidence-based practice guidelines in anticoagulation management that includes reversal strategies. As of July 1, 2019, The Joint Commission on Accreditation of Healthcare Organizations will require health systems to have approved evidence-based practice protocols for the reversal of anticoagulation and the management of bleeding events related to each anticoagulant medication.[15] The Anticoagulation Forum guideline will serve as a valuable tool for meeting the Joint Commission's National Patient Safety Goal for anticoagulant therapy (NPSG.03.05.01).

Antifibrinolytic agents have advantages such as low cost, availability, and low risk of thrombosis

OTHER SOCIETIES' RECOMMENDATIONS

Antifibrinolytic agents

In view of concerns about costs and side effects associated with reversal agents, some experts suggest using antifibrinolytic agents such as tranexamic acid and epsilon-aminocaproic acid for major bleeding (including life-threatening bleeding) and less serious bleeding with other comorbidities.[16] The use of antifibrinolytic agents was also recommended by the 2018 European Heart Rhythm Association guideline[13] and by *UpToDate*.[17] The advantages of these agents are their lower cost and ready availability, with minimal risk of thrombosis.

In addition to these agents, desmopressin can be used in settings of impaired platelet function associated with uremia or antiplatelet agents.[15] Dosing of desmopressin is 0.3 µg/kg subcutaneously, or intravenously in 50 mL of normal saline over 15 to 30 minutes (**Table 4**).[17] Only 2 doses are recommended due to concerns for tachyphylaxis and hyponatremia.[15]

A limitation of antifibrolytic agents is the lack of good quality clinical studies. However, a multicenter randomized clinical trial is currently enrolling patients to evaluate tranexamic acid for DOAC-associated intracerebral hemorrhage (ClinicalTrials.gov identifier NCT02866838).

There is also promising research on ciraparantag (PER977), which is a universal antidote for direct thrombin factor Xa inhibitors and heparinoids.[18]

SUMMARY

In summary, the Anticoagulation Forum guideline provides clear instructions on the use of 2 reversal agents, idarucizumab and andexanet alfa, for dabigatran-associated bleeding and direct factor Xa inhibitor-associated bleeding, respectively. The guideline also discusses the use of prohemostatic agents such as APPC and 4FPPC if idarucizumab and andexanet alfa are not available. Although it does not discuss the use of antifibrinolytic agents, it offers strategies for establishing and managing anticoagulation stewardship programs at the health system level.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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